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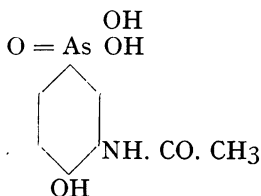
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A COMMENTARY ON CURRENT LITERATURE

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THE chemistry of stovarsol and its therapeutic use were discussed in the issue of this Journal for October, 1925. The view was then expressed that stovarsol was—so far as curing established syphilis and rendering a positive blood-Wassermann test permanently negative—inferior both to aresnobenzol and to bismuth, but of greater value than mercury. Its chief use was stated to be that of a prophylactic. Since that time a great deal of experience of this compound has been gained, especially on the Continent ; and the balance of opinion appears to agree with the above views.

Stovarsol—or *Spriozid*, as it is termed in Germany—was first prepared by Ehrlich, Benda and Bertheim.¹ It was thought by them to be oxyaminophenyl arsenious acid. The investigation was not pursued because of the toxicity of the compound and also because the arsenic in it exerts its pentavalent function. Ehrlich considered that the pentavalent arsenicals were therapeutically inferior to the trivalents such as the arsenobenzenes. Fournieu² reinvestigated the compound and prepared it in a high state of purity. He found that the toxicity noted by Ehrlich was due to impurities such as sodium arsenite. When the substance is properly synthesised it is represented by the formula :—



and is therefore *acetyl oxyaminophenyl arsinic acid*.

Stovarsol is administered by the mouth ; and Oppenheim³ summarises his experience of over 1,000 cases of

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syphilis so treated. He concludes that its first value is as a prophylactic ; that it is indicated in the treatment of infantile syphilis, in tertiary lesions of the pharynx and larynx, in grave cardio-vascular conditions, and in all instances where the administration of arsenobenzol is for any reason impossible or inadvisable.

The clue to its best use in the treatment of syphilis lies in appreciating the fact that it is a *pentavalent* arsenical. There are certain tissues for which pentavalent arsenic has an affinity, and these differ from the tissue affinities exhibited by trivalent arsenic. These facts have a vital bearing upon the treatment of syphilis, especially in its later stages, where the viscera are involved.

There appears to be general agreement as to the high prophylactic value of stovarsol, and the reason for this is apparently the predilection of pentavalent arsenic for ectodermal structures. By the administration of stovarsol an arsenical barrage is dropped upon the ectodermal threshold across which the *treponema pallidum* must step in order to gain admittance to the body. It is greatly to be regretted that stovarsol was not used as a prophylactic in the recent Shanghai Expeditionary Force. It is common knowledge that one of the great problems in that force was the high incidence of venereal disease among the troops. Whatever preventive measures were adopted, the oral administration of stovarsol was not one. The value of a prophylactic can best be assessed by studying its use in the Services ; and in the Shanghai Expedition an opportunity was certainly missed, not only for the testing of stovarsol, but for preventing much of the syphilis which occurred.

Stovarsol must be used with care, for cases of poisoning not infrequently occur. Bender ⁴ reviews this matter and gives details of six instances. The chief toxic signs are digestive disturbances such as diarrhoea and—rarely—vomiting, headache, cutaneous eruptions usually on the extensor surfaces of the limbs and presenting a diffuse erythema, dryness, and pruritus. Urticarial attacks are not infrequent. So far desquamative erythema does not seem to have been recorded. The cutaneous effects are probably largely nervous in origin, the erythemas and urticarias being caused by a toxæmia of the vasomotor nervous mechanism. In this they differ

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essentially from the severe erythema—often desquamative in character—which may occur after the administration of a trivalent arsenical. The trivalent arsenic seems to act directly upon the vessels. The increasing use of stovarsol in the treatment of malaria, yaws, and amœbiasis necessitates a warning note being sounded as to the possibility of toxic effects.

Since the appearance of stovarsol another compound for oral administration has been introduced by Flandin and Simon.⁵ This is the formyl derivative of oxyaminophenyl arsenic acid. It is sold under the name of *treparsol*. Its indications, advantages, disadvantages, and general properties coincide with those of stovarsol.

Osborne⁶ has completed some very interesting and painstaking microchemical studies of arsenic in arsenical dermatitis. These have a definite practical bearing for the syphilologist. In all the cases studied, the patients suffered from a dermatitis following the administration of arsenic. Sections were made of the affected skin, and these were stained with hæmalum. The amount of arsenic present varied directly with the severity of the dermatitis. The epidermis and horny layer of the skin were almost free from arsenic, as likewise was the sub-papillary layer of the corium. The greatest deposits were found deep in the corium around the arterioles and capillaries, in the walls of the sweat and sebaceous glands, and in the hair and hair-follicles.

An important observation made was that the site of arsenical deposition varied according as to whether the arsenic administered was in the trivalent or pentavalent form. In the former case, the arsenic showed a special affinity for the vascular structures, thus corroborating the clinical view that arsenobenzol is vasculo-toxic. Pentavalent arsenic, on the other hand, was specially attracted to ectodermal structures such as the various glands of the skin and the hair-follicles. A practical point arising from this is that the brain and spinal cord are ectodermal in origin, and the beneficial effect of a pentavalent arsenical—such as tryparsamide—in neurosyphilis would appear to be due to the valency of the arsenic. The pentavalents, then, are particularly indicated in the treatment of neurosyphilis, and they should be used in cases of cardio-vascular syphilis in preference to the trivalent arsenobenzols, which exert a

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directly deleterious effect upon such structures. Arsenobenzol is apt to do more damage, and do it more rapidly, to the wall of an aortic aneurism than to the treponemata residing therein.

As untoward effects, the pentavalent arsenicals are productive of pigmentation, musculo-spiral paralysis, optic atrophy, and slight dermatitis, the latter tending to occur, or at least to commence, on the extensor surfaces. The trivalents cause severe exfoliative dermatitis, purpura, and hæmorrhagic encephalitis. These seem to be the result of direct vascular injury, and the cutaneous signs are, as a rule, first observed on the flexor surfaces of the limbs.

In his inquiry, Osborne studied the effect upon arsenical dermatitis of sodium thiosulphate. Except in the very severe cases, this drug caused a rapid disappearance of arsenic from the skin. The lesson to be learned is that sodium thiosulphate must be administered early, before serious vascular damage has been done, and it must be pushed vigorously.

Osmond⁷ compares the Wassermann, Kahn and Sigma tests in which over 2,000 sera were investigated. He concludes that the results are definitely in favour of the Kahn, but at the same time he does not consider that it could or should replace the Wassermann. It is regarded as a useful additional test where the diagnosis is in doubt or where the Wassermann gives an indefinite result. He states that the Kahn gives a greater percentage of positives in cases of treated syphilis; in other words, that it remains positive longer than the Wassermann during treatment. In the sera examined, all three tests agreed in about 90 per cent. of cases. Disagreement occurred in 205 cases of syphilis, either treated or untreated. In those, the Kahn was most correct 160 times and the Wassermann 71 times. Since it is upon these 205 cases that the comparison must be made, it might apparently be legitimately argued that the result shows the Kahn test to be more than twice as good as the Wassermann and Sigma.

In discussing the relative value of these tests it is necessary to keep in mind the fact that, since the Wassermann was first in the field and has been longest in use, the basis of reference for the efficiency and accuracy of subsequent tests has tended to be the Wassermann

itself. There is an inclination to set up the Wassermann as an absolute standard by which the others are measured ; and therein lies a fallacy, inasmuch as if another test secures fewer positives than the Wassermann it is considered inefficient, while if it returns more positives these are regarded as being false, and the test is discarded as being inaccurate. The diagnosis of syphilis is often made by the Wassermann alone, and it is not therefore a sound procedure to judge the accuracy of another test according to its agreement or otherwise with the Wassermann.

Willett and Nagle⁸ claim for the Kahn a greater sensitiveness than the Wassermann during the early primary stage of syphilis, and they compare this test with the result of dark ground examination. Of 105 cases of primary syphilis 84 gave a positive Kahn, and in 64 the dark ground was also positive. In 39 the Kahn was positive and the dark ground negative. In 19 the Kahn was negative and the dark ground positive. The dark ground was found to be more accurate during the first week after the chancre, but subsequent to that time the Kahn test was the more reliable. The former gave 60 per cent. positive, and the latter 80 per cent. In 20 per cent. of cases the Kahn test failed, and in 39 per cent. the dark ground. It is not common for a positive Wassermann test to be obtained in the second and third weeks following the appearance of the chancre.

Hazen⁹ studied the diagnostic value of the Kahn in 2,600 cases in comparison with two Wassermann tests, one highly sensitive and the other more conservative in character. In primary syphilis the Kahn was the more sensitive ; in secondary syphilis the three ran parallel ; in tertiary cases the Kahn was the best ; in cerebro-spinal syphilis the Kahn was midway between the two Wassermans ; and in endosyphilis the Kahn was the best, as it also was in congenital syphilis.

Recently the Kahn has been substituted for the Wassermann in the routine work of the United States Naval Medical Service and in the Michigan State Laboratory, which is somewhat significant. It is very dangerous to allow the Wassermann to become the Mussolini of syphilitic diagnosis. The true standard by which serological tests must be measured is not with each other or with some selected individual similar test,

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but with clinical experience and bacteriological and histological examination.

If a personal view may be expressed, it is that the Kahn is a better and more accurate *routine* test than the Wassermann. It has a simpler technique, and there is less delay in obtaining a result. It is felt that the ideal routine test ought to be one which is highly sensitive, in which the result is rapidly obtained, and which can be carried out in the "side-room." To that test—whether it be the Kahn or some other—the Wassermann will be a useful complement.

Gabe¹⁰ records a case of *tabes dorsalis* and *gumma* of the testis in which all the clinical signs of these conditions were present, but the Wassermann test, both with respect to the blood and the cerebro-spinal fluid, was negative. Wisely the clinical diagnosis was accepted, and anti-syphilitic therapy was succeeded by excellent results. It cannot be too strongly emphasised that syphilis of the testis and epididymis is extremely common, although it seldom secures clinical recognition. Routine examination of the testes will reveal many cases in which there have been no symptoms to attract the patient's attention. In every case of enlargement of the testis or epididymis a blood-Wassermann test should be carried out; and even when a negative result is obtained, the therapeutic test is indicated. The histo-pathological work of Warthin at Ann Arbor has demonstrated how very frequently the testis is involved in syphilis. In the case recorded by Gabe, it is stated that "the Wassermann reaction of the blood, repeated six days after the provocative injection, . . . was negative." Had the provocative procedure been correctly carried out, the result might have been positive. In performing a provocative Wassermann test 0.3 or 0.45 gramme of an arsenobenzol compound is given intravenously, and the blood is tested every twenty-four hours thereafter for seven days. If syphilis is present a positive result is usually obtained during that period. In many cases the blood is positive in the first twenty-four hours, and may be again negative in forty-eight hours. It is useless to delay taking the blood till the sixth day after the injection.

REFERENCES

- (1) EHRLICH, BENDA and BERTHEIM. *Berichte d. deutsch. chem. Gesells.*, 1908, 1657.

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- (2) FOURNEAU. *Ann. de L'Inst. Pasteur*, XXXV., 571, 1922.
- (3) OPPENHEIM. *Ars Medici*, IV., 559, 1928.
- (4) BENDER. *Amer. Journ. Med. Sci.*, 819, Dec., 1927.
- (5) FLANDIN and SIMON. "Questions Actuelles de Syphil.," Paris, 1926.
- (6) OSBORNE. *Arch. Dermat. and Syph.*, July, 1928.
- (7) OSMOND. *Brit. Med. Journ.*, 440, March 17th, 1928.
- (8) WILLETT and NAGLE. *Journ. Amer. Med. Assoc.*, April 14th, 1928.
- (9) HAZEN. "Syphilis," 2nd ed., p. 514, Kimpton, London, 1928.
- (10) GABE. *Brit. Med. Journ.*, 102, July 21st, 1928.